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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,880	LIN, SHUO	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1,2,4-9 and 11-20 in the reply filed on 04/21/2006 is acknowledged. The traversal is on the ground(s) that restriction between two dependent inventions is not permissible. This is not found persuasive because the inventions are both independent and distinct. None of Groups I-VI is dependent, one upon another.

SDP 6/17/06

However, upon further examination of the application, it is deemed to not require an undue burden to search the product made by the elected method along with the method (Groups I and III). Furthermore, while Groups V and VII are inventions that are independent of Groups I and III that involve transgenesis, examination of the non-transgenic methods and product of Groups V,VI and VII does not require undue burden. Therefore, Groups I,III,V, VI and VII are rejoined. Groups II and IV, involving homologous recombination, do require additional search and the restriction between these groups is maintained.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claim 15 was included in Group I by error. In a phone conversation with William Wood on 06/06/2006, it was agreed that claim 15 should be omitted from Group I. Group I is directed to a method of introducing a transgene into a fish wherein the transgene is randomly inserted. Claim 15 is included in Group VI, which has been rejoined with Group I, however, Group VI is drawn to a method of cloning wherein a transgene inactivating an endogenous gene is already present in the progenitor fish to be cloned. Thus, claim 15 is under consideration as it relates to Group VI, but not to Group I.

Claims 1-21 are pending. Claim 3 is withdrawn as being drawn to a non-elected invention. Claims 1,2 and 4-21 are under consideration in the instant office action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The nucleic acids in Figure 7 require Sequencer Identifiers either in the figure itself or in the Brief Description of the Drawings. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Specification

The disclosure is objected to because of the following informalities: The priority information should be listed in the first line of the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2,4-9 and 11-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of making a diploid transgenic teleost fish comprising introducing an exogenous nucleic acid into the genome of a cultured embryonic fibroblast derived from a progenitor teleost embryo, transplanting the nucleus of the resulting transformed cell into an enucleated egg from a parental fish, wherein the parental fish is of the same species as the progenitor if fertile progeny are desired (claim 5), culturing the resultant embryo in conditions suitable for embryonic development such that a diploid transgenic fish is made and for 2) a method of making a teleost fish comprising obtaining a cell from a progenitor embryo, maintaining the cell in in vitro culture, transplanting the nucleus of the cultured cell into an enucleated egg from a parental fish of the same species as the progenitor and culturing the resultant embryo in conditions suitable for embryonic development such that a fertile progeny fish is made a does not reasonably provide enablement for a making any species of fish using any cell type or use of progenitor and parental fish of different species to make a fertile progeny. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims broadly encompass methods of making any species of fish, including live-bearing fish species. The claims also include use of any cell type, including differentiated cells from adult fish. The claims also broadly encompass use of a nucleus derived from a species that differs from the egg used in the method.

1) With respect to the species of fish encompassed by the claims, the specification is not enabling for all fish species, including live-bearing species. The specification teaches making transgenic zebrafish and prophetically teaches using the claimed transgenic methods for any fish species. The specification defines the claimed methods as being applicable to the variety of fish species that have been shown to be amenable to nuclear transplantation. However, the specification fails to define any parameters as guidance as to what fish species are amenable to nuclear transplantation. As such, the claims encompass any fish species, of which live-bearing fish are not enabled by the specification. One of skill in the art would not know how to culture an

egg made by the claimed methods using live-bearing species to obtain fish. Neither the specification nor the art of record teaches how to make any species of fish wherein the fish are born live and eggs and embryos develop internally inside female fish as encompassed by the claims. Therefore, claims should be limited in scope to teleost species of egg-laying fish where the egg structure is similar to that exemplified in the instant specification and the embryo develops externally (see specification at page 5, line 26-page 6, line 1).

2) With respect to the cell type used as a nuclear donor, the specification teaches use of isolated embryonic fibroblast cells (page 14, line 28-page 15, line 53). While the art of somatic cell nuclear transfer is highly underdeveloped as it relates to fish species, the art relating to mammalian species has set forth that necessary nuclear programming occurs with the greatest success using nuclei from fibroblast cells, especially fetal fibroblast cells. The art at the time of filing clearly recognized that some outside event to the donor cell in an NT procedure must occur for successful development of an NT unit. Both reprogramming and nuclear/nucleoli remodeling are events that the art regards as necessary for a cell to be completely totipotent, *i.e.,* for the cell to become competent to give rise to a live animal [Kono, **Reviews of Reproduction,** 2:74-80, 1997]. Fulka *et al.* [**Bioessays**, 20:847-851, 1998] state that the success when embryonic cells were used as nuclear donor was likely due to the embryonic cells not being completely differentiated at the time of transfer, and thus, amenable to undergo full reprogramming. Adult somatic cells would be less amenable to reprogramming. It is noted that some adult somatic cell types have been used to clone different mammalian species, however, the cell types and culture conditions are highly variable among species.

Furthermore, with respect to in vitro genetic modification of the cells, in a study of sheep

and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer [**Cloning and Stem Cells**, 3:221-231, 2001]. Thus, in light of the state of the art with regard to mammalian cloning and the teachings in the specification being limited to use of embryonic fibroblast cells, the specification is not enabling for the claimed methods using cells other than embryonic fibroblast cells.

Prior to the filing of the instant application, only early embryonic fish cells had been shown capable of reprogramming [Wakamatsu, PNAS, 98:1071-1076, 2001]. However, proper nuclear programming of adult somatic cells or non-fibroblast cells had not been demonstrated. The specification teaches use of embryonic fibroblast cells and does not teach that any other cell type or any adult-derived cell can be appropriately reprogrammed when transplanted into an enucleated egg. Therefore, the claims should be limited to the use of embryonic fibroblast cells as taught by the instant specification.

3) The claims fail to require that the recipient egg be of the same species as the nuclear donor. The specification is not enabling for cross-species nuclear transfer to obtain fertile offspring as required by claims 5 and 11-21. Sun *et al.* taught that cross-species nuclear transfer is effective in generating cloned fish, however, the offspring are infertile [**Biology of Reproduction**, 72:510-515, specifically page 513, column 1, paragraph 2]. Thus, the specification does not teach cross-species nuclear transfer as encompassed by the claims and does not enable such so as to produce fertile fish as required by claims 5 and 11-21.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6,7 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the embryo" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 is not clear because it is not known whether "derived from the embryo of the progenitor fish" is referring to an embryo that is progeny of a progenitor fish or a progenitor fish that is an embryo. Claim 7 depends from claim 6.

Claim 19 is not clear because it is not known whether "derived from an embryo of the progenitor fish" is referring to an embryo that is progeny of a progenitor fish or a progenitor fish that is an embryo.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, as obvious over Long *et al.* [1997, **Development**, 124:4105-4111].

Claim 10 is directed to a transgenic fish wherein the fish is made by the nuclear transfer method of claim 1. Claim 21 is directed to a progeny fish made by the nuclear transfer method of claim 11.

Claims 10 and 21 are product by process claims in which the process of creating the animal carries little patentable weight. It is only the product, which is anticipated by the prior art and not the process by which the product was made. This is because the final product (a transgenic fish) is not distinguished by any particular features or characteristics resulting from the process by which it is made. As such, the limitations of the claimed transgenic fish are met by any transgenic fish in the prior art. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re* Thorpe, 227 USPQ 964 (Fed. Cir. 1985).

Long *et al.* taught a transgenic zebrafish expressing a GFP reporter gene (Figure 3; page 4108, col. 2, paragraph 1), which is encompassed by the claimed transgenic fish of claim 10 and the progeny fish of claim 21. The transgenic fish, as taught by Long render the claimed fish obvious, because the claimed fish is not distinguishable over the instantly claimed fish.

Thus, the teachings of Long *et al.* anticipate the limitations of claims 10 and 21.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Examiner
Art Unit 1632

Application No.: 10/517880

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequences in figure 7 require sequence identifiers in the figures or in the Brief Description of the Drawings.

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE